SCIENTIFIC LETTER

Relation between birth weight and soluble markers of endothelial function in middle aged subjects

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The Barker hypothesis proposes that suboptimal fetal growth in utero results in metabolic programming leading to increased risk of diabetes, hypertension, and cardiovascular disease in adult life.[1] However, the magnitude of the impact of fetal programming on adult disease remains a focus of debate, and certainly our study of the Newcastle thousand families cohort of middle aged subjects found that adult lifestyle appears to have a substantially greater influence than low birth weight on the classic cardiovascular disease risk.[2]

The endothelium has a regulatory role in several mechanisms, including vascular tone and coagulation. Abnormalities of the endothelium have been found to predict cardiovascular disease, sometimes independent of the classic cardiovascular risk factors such as raised von Willebrand factor (vWF) concentrations.[3] Several studies have reported an association between low birth weight and different aspects of endothelial function.[4 5] The objective of this study was to determine whether soluble markers of endothelial function and inflammation are associated with low birth weight in middle aged subjects.

METHODS

The Newcastle thousand families study is a prospective cohort study of all 1142 children born in the city of Newcastle upon Tyne in May and June 1947. Birth weight measurements were obtained from records made by midwives. In 1996, 832 of the cohort were traced and 412 of them, representative of the original cohort, attended for a health check. From the 412 study members we generated a stratified sample of 120 subjects at the extremes of the birth weight distribution—that is, birth weight < 3.0 kg or birth weight > 3.8 kg. By studying the extremes of the birth weight distribution, we aimed at maximising the likelihood of finding a difference in the measures of endothelial function. From this stratified sample we contacted 82 subjects, of whom 74 were recruited into the study. Exclusion criteria for the study were intercurrent illness, blood disorders, and anticoagulant medication. The study was approved by the Newcastle upon Tyne local research ethics committee, and all subjects gave their informed consent.

Study participants were asked to avoid vigorous exercise or smoking for the preceding 24 or 12 hours, respectively, before assessment. Blood was sampled after an overnight fast. Anthropometric measures and glucose, insulin, lipids, and haemoglobin A1c concentrations were measured as previously described.[2] Soluble intracellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), and soluble E selectin (R&D Systems, Abingdon, UK) and vWF (Roche, Lewes, UK) were measured in duplicate by commercial assays. High sensitivity C reactive protein (hs-CRP) was measured by an enzyme linked immunosorbent assay (ELISA) method.

Groups were compared by non-paired *t* tests and analysis of covariance. Data were log transformed to normalise distributions. A value of $p < 0.05$ was considered significant.

RESULTS

Of the 74 study members recruited, four were excluded: from the lower birth weight group, one due to treatment with warfarin and two due to diabetes, and from the higher birth weight group, one due to intercurrent illness. Of the remaining 70 subjects, 35 were in the lower and higher birth weight groups. As table 1 summarises, all participants were 54 years old at the time of study and sex distribution was comparable between the groups. The groups did not differ in smoking status, body mass index, waist to hip ratio, blood pressure, or glucose and lipid concentrations. However, the lower birth weight group had higher fasting insulin concentrations and homeostasis model assessment-insulin resistance (HOMA-IR) index (both $p < 0.05$) than the higher birth weight group. A higher frequency of participants in the lower birth weight group reported previously diagnosed hypertension, hyperlipidaemia, and ischaemic heart disease (data not shown), although the actual number of participants involved was very small. Few study participants were taking angiotensin converting enzyme inhibitors (three subjects in each group) and statins (six versus two in the lower and higher birth weight groups, respectively). As table 1 shows, the groups did not differ in vWF, soluble E selectin, sVCAM, sICAM, and hs-CRP.

DISCUSSION

Birth weight did not predict circulating concentrations of markers of endothelial cell activation or damage in this study population, and our results differ from the findings of other studies that have explored the same question. A study of young adults (aged 20–28 years) found that low birth weight predicted endothelial function assessed by nitric oxide dependent flow mediated dilatation, but only in subjects with a low cardiovascular risk based on the classic risk factors (smoking, serum cholesterol, obesity).[5] McAllister *et al*[4] similarly studied a group of young adults (mean age 28 years) but found that nitric oxide dependent vascular reactivity was normal in the low birth weight group. However, the low birth weight subjects did have significantly higher vWF concentrations. Why were we unable to replicate this finding, considering that we had almost three times as many subjects in each subject group? One possible explanation is that their low birth weight cut off was more stringent (< 2.5 kg *v* < 3.0 kg), although the mean differences between the birth weight groups were comparable between the two studies (1.1 kg and 1.4 kg). A much more likely explanation is that our cohort was much older, with all subjects aged 54 years. Our subjects would have experienced a greater burden of lifestyle factors that may well have overwhelmed any residual effect of fetal programming on endothelial function. This is in keeping with our earlier

Abbreviations: ELISA, enzyme linked immunosorbent assay; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high sensitivity C reactive protein; sICAM, soluble intracellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; vWF, von Willebrand factor

Table 1 Characteristics of study participants

Characteristic	Lower birth weight (<3 kg)	Higher birth weight (>3.8 kg)	Difference between groups (95% CI)	p Value
Birth weight (kg)	2.77 (0.18)	4.17 (0.26)	1.39 (1.28 to 1.50)	<0.001
Sex	M = 15, F = 20	M = 18, F = 17	NA	NS
Age (years)	54	54	NA	NS
Body mass index (kg/m^2)	26.9 (4.36)	25.9 (4.14)	1.02 (−1.10 to 2.97)	0.36
z Score waist to hip ratio	0.02 (0.98)	−0.02 (1.02)	0.05 (−0.40 to 0.51)	0.81
Insulin sensitivity				
Fasting glucose (mmol/l)*	5.3 (5.0, 5.8)	5.1 (4.9, 5.5)	0.01 (−0.01 to 2.91)	0.27
Fasting insulin (mU/l)*	8.0 (6.4, 12.1)	6.2 (4.5, 9.2)	0.11 (0.07 to 0.24)	0.04
HOMA index*	1.9 (1.5, 2.8)	1.4 (0.9, 2.3)	0.14 (0.04 to 0.28)	0.04
Lipid status				
Cholesterol (mmol/l)	5.6 (0.9)	5.6 (1.3)	−0.09 (−0.64 to 0.45)	0.72
LDL (mmol/l)	3.4 (0.8)	3.6 (1.2)	−0.27 (−0.75 to 0.20)	0.25
HDL (mmol/l)	1.4 (0.5)	1.4 (0.4)	0.03 (−0.19 to 0.25)	0.80
Triglycerides (mmol/l)*	1.5 (0.9, 2.4)	1.2 (0.8, 1.5)	0.10 (−0.01 to 0.2)	0.07
Measured BP				
Systolic BP (mm Hg)	133.9 (19.2)	127.0 (13.9)	6.94 (−1.06 to 14.94)	0.08
Diastolic BP (mm Hg)	81.4 (9.2)	79.1 (8.4)	2.26 (−1.94 to 6.45)	0.29
Soluble markers				
vWF (IU/l)*	959 (805, 1224)	1044 (791, 1296)	0.007 (−0.07 to 0.08)	0.86
Soluble E selectin (ng/ml)*	59.0 (43.0, 68.5)	56.0 (41.0, 64.0)	0.03 (−0.11 to 0.04)	0.38
sVCAM (ng/ml)*	450.0 (382.5, 571.5)	500.0 (439.5, 546.0)	−0.01 (−0.02 to 0.06)	0.42
sICAM (ng/ml)*	314.0 (259.0, 395.0)	308.0 (276.0, 363.0)	0.003 (−0.05 to 0.04)	0.88
hs-CRP (mg/l)*	19.5 (8.1, 48.6)	18.4 (7.6, 37.3)	0.11 (−0.13 to 0.36)	0.36

Data are mean (SD).*
Skewed data were log transformed before *t* testing and are presented as the median (25/75th interquartiles).
BP, blood pressure; CI, confidence interval; F, female; HDL, high density lipoprotein; HOMA, homeostasis model assessment; hs-CRP, high sensitivity C reactive proteins; ICAM, soluble intracellular adhesion molecule; LDL, low density lipoprotein; M, male; NA, not applicable; NS, not significant; sVCAM, soluble vascular cell adhesion molecule; vWF, von Willebrand factor.

observation that adult lifestyle exerted a substantially greater influence than birth weight on the classic cardiovascular disease risk in this same cohort.[2] It is also supported by the observation of Leeson *et al*,[5] as the relation between low birth weight and endothelial function was not apparent in patients with an established adverse cardiovascular risk profile.

We confirmed what other groups have reported: that low birth weight is associated with insulin resistance (increased fasting insulin concentrations and HOMA-IR). However, the relation was comparatively weak, with body mass index and birth weight accounting for 39% ($p<0.001$) and 4% ($p = 0.06$), respectively, of the variance in fasting insulin concentrations.

In conclusion, therefore, a relation between low birth weight and soluble markers of endothelial function was not apparent in our cohort of middle aged subjects. In this age group, lifestyle factors are likely to be the major determinants of endothelial function.

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